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Intrauterine Device Use and Endometrial Cancer Risk

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Sturgeon S R (Environmental Epidemiology Branch, National Cancer Institute, 6130 Executive Boulevard, EPN443, Bethesda, MD 20852, USA), Brinton L A, Berman M L, Mortel R, Twiggs L B, Barrett R J, Wilbanks G D and Lurain J R. Intrauterine device use and endometrial cancer risk. *International Journal of Epidemiology* 1997: **26:** 496–500.

Background. Because intrauterine devices (IUD) invoke acute and chronic inflammatory responses in the endometrium, it is possible that prolonged insertion of an IUD could induce endometrial cancer.

Methods. We examined the relation between use of an IUD and endometrial cancer risk using data from a multicentre case-control study involving 405 endometrial cancer cases and 297 population controls.

Results. A total of 20 (4.9%) cases and 34 (11.4%) controls reported any use of an IUD. After adjustment for potential confounders, IUD use was not associated with an increased risk of endometrial cancer (RR = 0.56 for ever use; 95% CI : 0.3–1.0). Little reduction in risk was observed among women who last used an IUD within 10 years of the index date (RR = 0.84; 95% CI : 0.3–2.4) but risk was decreased among women who used an IUD in the more distant past (RR = 0.45; 95% CI : 0.2–1.0). Risk did not vary consistently with number of years of IUD use or with years since first use. Risk was not increased among women who used inert devices (RR = 0.46; 95% CI : 0.3–3.6) or those who used devices containing copper (RR = 1.08; 95% CI : 0.1–3.6).

Conclusion. These data are reassuring in that they do not provide any evidence of an increased risk of endometrial cancer among women who have used IUD.

Keywords: intrauterine device (IUD), endometrial cancer, contraception, epidemiology

Because intrauterine devices (IUD) invoke acute and chronic inflammatory responses in the endometrium, it is possible that prolonged insertion of an IUD could induce endometrial cancer.[1] IUD containing copper may be particularly suspect because they tend to produce more serious endometrial irritation than inert devices.[2] IUD could also theoretically increase endometrial cancer risk because they alter uterine sensitivity to oestrogen and progesterone.[3]

Although IUD are used by an estimated 85 million women worldwide,[4] only four small studies have examined the relation between their use and the occurrence of endometrial cancer[5–8] and none were able to examine risks associated with specific types of IUD. Thus, we used data from a large multicentre case-control study in the US to evaluate further the relation between IUD use and endometrial cancer.

METHODS

This case-control study was a collaborative effort with seven participating hospitals in five areas of the US—Chicago, Illinois; Hershey, Pennsylvania; Irvine and Long Beach, California; Minneapolis, Minnesota; and Winston-Salem, North Carolina. A total of 498 women between the ages of 20 and 74 years with newly diagnosed endometrial cancer were identified between 1 June 1987 and 15 May 1990. Detailed information on the selection of cases and controls and other study methods are presented elsewhere.[9] Briefly, random digit dialling techniques were used to select controls for cases younger than age 65 whereas older controls were selected using information provided by the Health Care Financing Administration. We attempted to select one control for each case, matched for age (5-year age groups), race, and location of residence at diagnosis (telephone exchange or zip code).

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Random digit dialling controls were selected by identifying a residential cluster matched for the telephone exchange for each eligible case. Telephone numbers were called, and an enumeration of female members aged 20–64 in each household was attempted. Of 15 820 telephone numbers sampled, 10 184 were assessed to be residential working numbers, and an enumeration of female members was obtained for 85%. Older controls were derived from Health Care Financing Administration computer records a subject of the same age, race and zip code as each eligible case. After the initial selection of subjects, a short telephone questionnaire was administered to determine whether the subjects had intact uteri. A total of 125 of the initially selected random digit dialling controls and 88 of the Health Care Financing Administration controls were eliminated because of their not being at risk of developing endometrial cancer. These subjects were replaced with other eligible controls so that there was an eventual accrual of 304 controls through random digit dialling techniques and 173 through Health Care Financing Administration records.

Trained interviewers completed home interviews on 434 (87%) of the eligible cases and 313 (66%) of the eligible controls. Eligible subjects who could not be interviewed were not replaced. Reasons for non response included refusal (5% of the cases and 22% of the controls), communication problems (4% versus 3%) and other problems (2.2% versus 9%). In addition, physician consent was not obtained for 2.0% of the cases. The response rate was considerably higher for the random digit dialling than the Health Care Financing Administration controls (76% vs 47%).

Pathology reports were obtained and reviewed for all cases, with 93% of the interviewed cases having a classification of epithelial cancer. Because of the distinct epidemiological characteristics of sarcomas,[10] this analysis focused on data from interviews with 405 epithelial cancer cases and their 297 matched controls. The mean ages of the cases and controls were 59.2 (standard deviation [SD] = 9.96) and 58.0 years (SD = 10.4), respectively.

A structured interview, on average 76 minutes in length, was administered to obtain information on hypothesized risk factors, including demographics, pregnancy history, menstrual history, contraceptive behaviour, use of exogenous hormones, changes in body weight, diet and alcohol intake, family history of cancer, medical events and physical activity. The dietary section consisted of 60 food items and provided an estimate of usual adult caloric intake and intake of specific nutrients.[11] Anthropometric measurements, including waist-to-thigh circumference ratio as a measure of intra-abdominal fat,[12] were also taken at the time of interview. Information on birth control usage was obtained using lifetime calendars to record usage of specific methods on a monthly basis. For each mention of IUD use, information on brand was elicited. No subjects reported using progestagen containing IUD.

Because of the large number of cases without an interviewed matched control, adjusted maximum likelihood relative risk estimates (RR) and 95% confidence intervals (CI) are presented using unconditional logistic regression techniques.[13] The main results of the study were confirmed using conditional logistic regression on the smaller subset of 274 matched pairs of cases and controls.

Risk factors identified in this study, adjusted for each other, included education (RR = 2.0 for $\geqslant$16 versus $<$12 years), age at menarche (RR = 2.8 for $<$12 versus $\geqslant$15 years), menopausal oestrogen use (RR = 15.3 for $\geqslant$10 versus 0 years), diabetes (RR = 1.6), saturated fat intake (RR = 2.0 for highest versus lowest quartile), current body mass index (weight in kg/height in m^2) (RR = 3.2 for $\geqslant$32 versus $<$25) and waist to thigh circumference (RR = 2.7 for highest versus lowest quartile). Factors associated with reductions in risk included multiple livebirths (RR = 0.2 for $\geqslant$5 versus 0 births), cigarette smoking (RR = 0.3 for current versus never smokers), and oral contraceptive use (RR = 0.4 for $\geqslant$5 versus 0 years). Menopausal status and age at natural menopause were unrelated to risk.[9]

RESULTS

Table 1 presents the prevalence of risk factors among controls who never used any method of birth control, those who ever used an IUD and those who only used other forms of birth control. Compared to women who had never used any method of birth control, women who had used an IUD were younger, better educated and had a higher intake of saturated fat. Women who had used an IUD also had a lower waist to thigh circumference ratio, and were less likely to smoke and to be nulliparous. Differences tended to be less striking between women who had ever used an IUD and those who had only used other forms of birth control. Compared to those who only used other forms of birth control, women who had used an IUD were younger, better educated, had a later age at menarche and a lower waist to thigh circumference ratio. A total of 27 (79.4%) of the 34 controls who had ever used an IUD also had taken oral contraceptives (data not shown).

A total of 20 cases (4.9%) and 34 controls (11.4%) reported any use of an IUD, resulting in an age-adjusted relative risk of 0.43 (95% CI : 0.2–0.8). Further adjustment for oral contraceptive use attenuated this reduction

TABLE 1 *Characteristics of controls by their birth control practices*

Characteristic	Never used birth control[a] (n = 86)	Ever used birth control	
		IUD users (n = 34)	Non-IUD users[b] (n = 177)
Age			
<50	3 (3.5)	15 (44.1)	37 (20.9)
⩾50	83 (96.5)	19 (55.9)	140 (79.1)
Education			
<12	38 (44.2)	5 (14.7)	33 (18.6)
12	20 (23.3)	5 (14.7)	66 (37.3)
13–15	11 (12.8)	9 (26.5)	40 (22.6)
⩾16	17 (19.8)	14 (41.2)	36 (20.3)
Unknown	0 (0.0)	1 (2.9)	2 (1.1)
Saturated fat intake			
Q1 (low)	29 (33.7)	5 (14.7)	40 (22.6)
Q2	18 (20.9)	9 (26.5)	46 (26.0)
Q3	22 (25.6)	8 (23.5)	45 (25.4)
Q4 (high)	17 (19.8)	11 (32.4)	46 (26.0)
Unknown	0 (0.0)	1 (2.9)	0 (0.0)
Waist to thigh circumference			
Q1	12 (14.0)	11 (32.4)	45 (25.4)
Q2	19 (22.1)	9 (26.5)	43 (24.3)
Q3	24 (27.9)	5 (14.7)	40 (22.6)
Q4	25 (29.1)	7 (20.6)	38 (21.5)
Unknown	6 (7.0)	2 (5.9)	11 (6.2)
Age at menarche			
>13	20 (23.3)	6 (17.6)	62 (35.0)
13	31 (36.0)	13 (38.2)	46 (26.0)
⩽12	34 (39.6)	15 (44.1)	68 (38.4)
Unknown	1 (1.2)	0 (0.0)	1 (0.6)
Cigarette smoker			
Never	51 (59.3)	17 (50.0)	105 (59.3)
Former	13 (15.1)	11 (32.4)	43 (24.3)
Current	22 (25.6)	6 (17.6)	29 (16.4)
Number of livebirths			
0	20 (23.3)	1 (2.9)	7 (4.0)
1–2	26 (30.2)	17 (50.0)	75 (42.4)
3–4	22 (25.6)	12 (35.3)	58 (32.8)
⩾5	18 (20.9)	4 (11.8)	37 (20.9)
Diabetes			
No	78 (90.7)	34 (100.0)	164 (92.7)
Yes	8 (9.3)	0 (0.0)	13 (7.3)
Menopausal oestrogens[c]			
No	74 (89.2)	16 (84.2)	111 (79.3)
Yes	9 (10.8)	2 (10.5)	28 (20.0)
Unknown	0 (0.0)	1 (5.3)	1 (0.7)
Body mass index (kg/m^2)			
<25	42 (48.8)	17 (50.0)	88 (49.7)
25–28	18 (20.9)	8 (23.5)	48 (27.1)
⩾29	21 (24.4)	9 (26.5)	41 (23.2)
Unknown	5 (5.8)	0 (0.0)	0 (0.0)

[a] No method of birth control except the rhythm method or withdrawal.
[b] Includes users of oral contraceptives, barrier methods of contraception, spermicides, women who were sterilized and women whose partners were sterilized.
[c] Restricted to women ⩾50 years.

TABLE 2 *Risk of endometrial cancer associated with use of an intrauterine device*

	Cases (n = 405)	Controls (n = 297)	Adjusted[a] RR (95%CI)
Years of use			
Never[b]	385	263	1.0
Ever	20	34	0.56 (0.3–1.0)
⩽3 years	10	17	0.53 (0.2–1.3)
>3 years	10	17	0.60 (0.2–1.5)
Years since first use			
Never[b]	385	263	1.0
⩽15 years	5	9	0.54 (0.2–2.0)
>15 years	15	25	0.57 (0.3–1.2)
Years since last use			
Never[b]	385	263	1.0
⩽10 years	9	10	0.84 (0.3–2.4)
>10 years	11	24	0.45 (0.2–1.0)
Type of device[b]			
None	385	263	1.0
Copper[c]	9	10	1.08 (0.3–3.6)
Inert only	9	24	0.46 (0.1–3.6)
Unknown	2	0	

[a] Adjusted for age (5-year age categories), education (<12, 12, 13–15, ⩾16), dietary intake of saturated fat (Q1–Q4), waist to hip circumference ratio (Q1–Q4), age at menarche (<12, 12, 13, 14, ⩾15), cigarette smoking (never, current, former), number of livebirths (0, 1–2, 3–4, ⩾5), and years of oral contraceptive use (0, <4, ⩾4).
[b] Includes women who never used any form of birth control and those who used any form of birth control except an intrauterine device.
[c] Includes two cases and three controls who also used inert devices.

in risk (RR = 0.53, 95% CI : 0.3–1.0). After further controlling for the other potential confounders identified in Table 1 (education, intake of saturated fat, waist to thigh circumference ratio, number of livebirths, cigarette smoking, and age at menarche), risk remained modestly lowered among women who used an IUD (RR = 0.56; 95% CI : 0.3–1.0) (Table 2). In this fully-adjusted model, risk did not vary with increasing years of use and years since first IUD use was unrelated to risk of endometrial cancer. Risk did, however, appear to vary by years since last IUD use. Little reduction in risk was observed among women who last used an IUD within 10 years of the index date (RR = 0.84; 95% CI : 0.3–2.4) but risk was reduced among those who last used an IUD more than 10 years before (RR = 0.45; 95% CI : 0.2–1.0).

IUD were also categorized into two groups for analysis based on the presence or absence of copper. Inert device use was associated with a reduction in risk (RR = 0.46; 95% CI : 0.1–3.6) whereas copper device use was unrelated to risk (RR = 1.08; 95% CI : 0.3–3.6). The small number of IUD users precluded further

stratification to investigate the separate effects of years since last use and type of IUD device on risk.

Additional adjustment for diabetes, current body mass index, cigarette smoking, menopausal oestrogen use, use of barrier methods of contraception, spermicides, female sterilization, and vasectomy of a partner did not materially change the risk estimates presented in Table 2. Excluding 86 women who had never used any form of birth control from the referent category also did not alter the results. Women who had used an IUD remained at modestly reduced risk of endometrial cancer (RR = 0.67; 95% CI : 0.3–1.6) in a separate analysis that excluded 188 women who had ever used oral contraceptives.

Because IUD were first commercially available in the US in 1964, few of the women 65 years and older in this study would have had an opportunity to use IUD. Results were similar when we restricted the above analyses to women younger than 65 years.

DISCUSSION

Three of four previous studies have observed a modest overall reduction in endometrial cancer risk among women who had ever used an IUD.[5–7] No evidence of a positive relation between IUD use and risk was found among women under age 55 in an analysis of data from the Cancer and Steroid Hormones (CASH) study (RR = 0.5 for ever use versus none; 95% CI : 0.3–0.8).[5] In the analysis of data from a case-control study in Italy,[6] the relative risk associated with ever use of an IUD was 0.4 (95% CI : 0.1–1.0). A study carried out in developing countries also reported no increased risk associated with use of an IUD (RR = 0.7 for ever use versus none; 95% CI : 0.4–1.3).[7] One conducted in Shanghai, China found no relationship between IUD use and endometrial cancer risk (RR = 1.1 for ever use; 95% CI : 0.5–2.5).[8]

With respect to type of IUD device, we did not find any evidence of an increased risk of endometrial cancer among women who used either inert devices or those who used devices containing copper.

Studies have been inconsistent with respect to their findings on the effects of years of IUD use and years since last IUD use on risk. In the present investigation, the reduction in risk associated with IUD use was apparent only among women whose use had ceased more than 10 years ago. In the CASH study conducted in the early 1980s,[5] however, risk did not vary by time elapsed since last IUD use. By contrast, Rosenblatt *et al.*[7] found that risk was lowest among current users (RR = 0.1; 95% CI : 0.01–0.8). In accord with the study by Rosenblatt *et al.*[7] we found no evidence that risk decreased with increasing years of IUD use. Castellsague *et al.*[5] however, observed that risk decreased from 0.62 among women who used IUD for less than 4 years to 0.41 for those who used an IUD for more than 8 years. No details were available on the relation between risk and various exposure measures from the other two studies.[6–8]

It is unclear why relationships with years since last IUD use and years of IUD use have differed across studies. This inconsistency may reflect the difficulty in obtaining stable risk estimates from studies involving small numbers of IUD users. Another possible explanation relates to the fact that the materials and shapes of IUD devices have varied across populations and calendar time.[5] If certain IUD have more of an effect on endometrial cancer risk, studies conducted in different populations could observe disparate findings. Alternatively, the lack of consistency across studies may indicate that the modest reduction in risk associated with IUD use is the result of indication bias. Such bias could result if women at increased risk of developing endometrial cancer were less likely to be prescribed IUD (e.g. those with uterine bleeding from endometrial hyperplasia).

The major limitation of the present study is that the response rate was low among the population-based controls. If the controls who were IUD users were disproportionately more likely to be interviewed than cases, this could result in a spurious reduction in risk associated with IUD use. It is somewhat reassuring, however, that findings from this study with respect to generally accepted endometrial cancer risk factors, are similar to those presented in previous studies.[14]

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